Antiinflammatory Properties of Hepatic Acute Phase Proteins: Preferential Induction of Interleukin 1 (IL-1) Receptor Antagonist over IL-1β Synthesis by Human Peripheral Blood Mononuclear Cells

By Herbert Tilg,* Edouard Vannier,‡ Gloria Vachino,*
Charles A. Dinarello,‡ and James W. Mier*

*From the *Divisions of Hematology-Oncology and ‡Infectious Disease, Department of Medicine, New England Medical Center and Tufts University School of Medicine, Boston, Massachusetts 02111*

Summary

This study was undertaken to determine whether acute phase proteins (APP) induce the synthesis of interleukin 1β (IL-1β) and its specific antagonist, IL-1 receptor antagonist (IL-1Ra), in human peripheral blood mononuclear cells (PBMC). PBMC from healthy volunteers were incubated with C-reactive protein (CRP), α_1-antitrypsin (α_1-AT), or α_1-acid glycoprotein (AGP), and the levels of IL-1β and IL-1Ra produced were measured by specific radioimmunoassay. To evaluate the effects of α_1-AT further, a synthetic pentapeptide FVYLI corresponding to the minimal binding sequence for the serpine–enzyme complex receptor was also evaluated. PBMC incubated for 24 h with CRP, α_1-AT, or the pentapeptide FVYLI synthesized large quantities of IL-1Ra, 5–10-fold greater than the amount of IL-1β produced by these cells. AGP induced significantly less IL-1Ra than the other APP tested. These effects were shown to be specific, in that polyclonal antibodies against CRP, α_1-AT, and AGP eliminated the cytokine production induced by these respective proteins. CRP, α_1-AT, FVYLI, and AGP were synergistic with low concentrations of endotoxin in the induction of both IL-1Ra and IL-1β synthesis. We suggest that the preferential induction of IL-1Ra by APP may contribute to their antiinflammatory effects and provide an important regulatory signal for the acute phase response.

The liver is thought to play a central role in limiting local and systemic inflammation. D-Galactosamine, an hepatocyte-specific inhibitor of RNA and protein synthesis, sensitizes animals to the lethal effects of endotoxin or TNF-α, suggesting that proteins synthesized in the liver in response to inflammatory mediators attenuate their biological effects (1). The acute phase response induced by turpentine administration protects mice from D-galactosamine/endotoxin and D-galactosamine/TNF-α–induced death (2).

In some instances, specific hepatic acute phase proteins (APP)[1] synthesized in response to infection or tissue injury have been demonstrated to protect animals from various inflammatory insults. For example, transgenic mice expressing rabbit C-reactive protein (CRP) resist endotoxemia (3). Rabbits with elevated serum CRP induced by croton oil injections exhibit diminished neutrophil infiltration and vascular permeability in a C5a-induced alveolitis model (4). Serum amyloid A attenuates IL-1– and TNF-α–induced fever and hypothalamic PGE_2 synthesis in mice (5). Both α_1-antitrypsin (α_1-AT) and antichymotrypsin inhibit neutrophil superoxide production (6, 7), which may contribute to the protective effect of α_1-AT on the development of bleomycin-induced pulmonary fibrosis (8). Furthermore α_1-AT protects cultured lung endothelial cells from endotoxin injury (9). The mechanisms by which APP protect against inflammation are generally not understood.

IL-1 plays a key role in inflammatory and growth processes. IL-1 is an important mediator of fever, hypotension, and the acute phase reaction (10). A specific inhibitor of IL-1 has been identified and its cDNA has been cloned (11–13). This inhibitor is closely related to IL-1α and IL-1β and competitively blocks the binding of IL-1 to its receptors (12, 13). This IL-1 receptor antagonist (IL-1Ra) has no agonist activity (14) and efficiently blocks IL-1 effects both in vitro and in vivo (12, 13). IL-1Ra has been shown to reduce the severity of sepsis, arthritis, colitis, and other inflammatory processes in several animal models (12, 13).

In this investigation, we sought to determine whether or not the antiinflammatory effects of certain hepatic APP could be attributed to a modulation in the profile of cytokines pro-

[1] *Abbreviations used in this paper:* AGP, α_1-acid glycoprotein; APP, acute phase protein(s); α_1-AT, α_1-antitrypsin; CRP, C-reactive protein; IL-2Ra, IL-2 receptor antagonist; SEC, serpine–enzyme complex.

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duced in response to noxious stimuli or to the induction of cytokine antagonists.

Materials and Methods

Reagents. Purified human α_1-acid glycoprotein (AGP), α_1-AT, human leukocyte elastase, LPS from *Escherichia coli* (055:B5), goat and rabbit IgG, DMSO, and polyethylene glycol of 8,000 mol wt were purchased from Sigma Chemical Co. (St. Louis, MO). Rabbit polyclonal anti–human AGP and anti–human α_1-AT IgG were also obtained from Sigma Chemical Co. A polyclonal goat anti–human CRP IgG was purchased from BIODESIGN Int. (Kennebunkport, ME). IL-2 was provided by Cetus/Chiron (Emeryville, CA). A neutralizing rabbit IgG against human IL-2 and an anti–p75 IL-2 receptor mAb were gifts from Endogen Inc. (Boston, MA). Polymyxin B sulfate was purchased from Pfizer Inc. (New York).

α_1-AT–elastase complexes were prepared according to previously described methods by incubating equimolar concentrations of α_1-AT and elastase at 37°C for 15 min (15). The peptides FVYL and FVYLI (provided from M. Berne, Department of Physiology, Tufts University School of Medicine, Boston) were synthesized by solid-phase method and then HPLC purified. Both peptides were dissolved in DMSO before use. CRP was isolated from serum of patients treated with high-dose IL-2 using phosphorylcholine-Sepharose affinity chromatography (16). SDS-PAGE of the purified material revealed a single protein band. The LPS content of the various protein and peptide preparations used in these studies was determined by a *Limulus* amebocyte lysate assay (Associates of Cape Cod, Inc., Woods Hole, MA). CRP and FVYLI stock solutions were negative (<10 pg/ml) in these assays. The LPS content of the AGP and α_1-AT preparations varied but was <10 pg/ml at the dilutions used in the LPS synergy studies described in Results.

PBMC Cultures. PBMC were isolated from the heparinized blood of healthy donors by centrifugation through Ficoll Hypaque (Sigma Chemical Co.). The cells were washed three times with sterile PBS and then incubated in polypropylene tubes (5 ml) at a density of 2.5×10^6 cells/ml in 1 ml of RPMI 1640 medium (GIBCO, Grand Island, NY), containing 10 mM Hepes (Sigma Chemical Co.), 2 mM L-glutamine, 100 U/ml penicillin, and 100 μg/ml streptomycin (Irvine Scientific, Santa Ana, CA). Complete medium was subjected to ultrafiltration to remove endotoxin and other cytokine-inducing materials (17). Polymyxin B (5 μg/ml) was included in all culture medium except that used in experiments with LPS. PBMC were incubated with CRP, α_1-AT, FVYL, FVYLI, AGP, or LPS at 37°C in a humidified atmosphere containing 5% CO_2 for 24 h unless stated otherwise. PBMC cultures were frozen and thawed three times (18). The amount of IL-1β and IL-1Ra reported in these experiments therefore represents the total amount (secreted plus cell-associated) generated.

RIAs. Specific RIAs for IL-1Rα and IL-1β were used in each study (18, 19). The threshold of detection for both assays was 80–160 pg/ml.

Statistics. All data are expressed as mean ± SEM. Two-tailed paired *t* tests and analysis of variance (ANOVA) using Fisher's least significant difference were used. *P* values <0.05 were considered to be significant.

Results

Induction of IL-1Ra and IL-1β Synthesis in Human PBMC by CRP. The induction of IL-1Ra and IL-1β by CRP after a 24-h incubation period is shown in Fig. 1. A concentration of as low as 50 μg/ml CRP induced significantly more IL-1Ra (1.9 ± 0.3 ng/ml) than did control medium (0.35 ± 0.1 ng/ml) (*P* <0.05). Induction of IL-1Ra by CRP was concentration dependent and maximal at 300 μg/ml CRP. In contrast, CRP induced IL-1β only at the highest concentration tested (300 μg/ml) (*P* <0.05). The amount of IL-1Ra produced by PBMC at a CRP concentration of 300 μg/ml was nearly 10-fold the amount of IL-1β produced.

We next studied the time course of IL-1Ra and IL-1β production in response to CRP. A concentration of 300 μg/ml CRP was used in these experiments. Freshly isolated PBMC contained neither measurable IL-1Ra nor IL-1β. After a 2-h incubation, low levels of IL-1Ra were detectable. Significant amounts of IL-1Ra (1.4 ± 0.20 ng/ml) were measurable after a 4 h incubation and peak levels of IL-1Ra (11.8 ± 1.2 ng/ml) and IL-1β (1.5 ± 0.23 ng/ml) were obtained after 24 h (Fig. 2).

To rule out the possibility that the effects observed with CRP were due to endotoxin contamination, PBMC were incubated with CRP in the presence or absence of an anti–CRP antibody or polymyxin B. As shown in Table 1, anti–CRP antibodies, but not control antibodies, completely blocked CRP-induced IL-1Ra and IL-1β synthesis, whereas LPC-induced IL-1Ra and IL-1β production was not affected. In parallel experiments, polymyxin B (5 μg/ml) completely abolished LPS-induced but not CRP-induced cytokine production (Table 1).

IL-2 induces both IL-1β and IL-1Ra in vitro (20, H. Tilg, manuscript submitted for publication). Because the CRP used in our studies was purified from sera obtained from patients undergoing IL-2 treatment, it was essential to demonstrate that our CRP preparation did not contain residual IL-2, which could contribute to the IL-1Ra and IL-1β production attributed to CRP. PBMC stimulated with IL-2 or CRP were incubated with an anti–IL-2 or anti–p75 IL-2 receptor IgG and the production of IL-1Ra and IL-1β measured. Both anti-

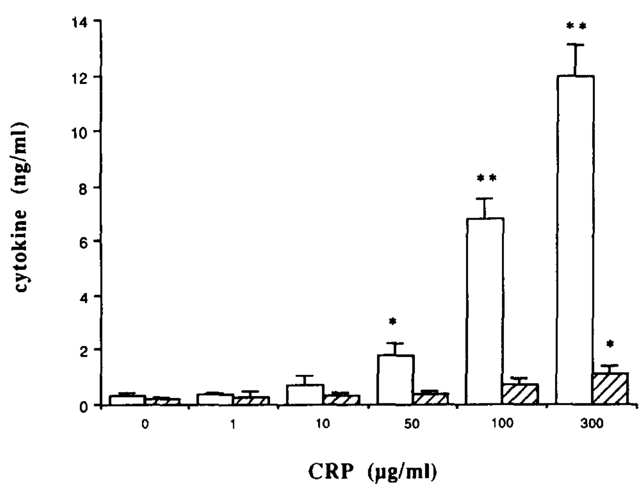

Figure 1. Induction of IL-1Ra (*open bars*) and IL-1β (*hatched bars*) by human PBMC from six donors incubated with increasing concentrations of CRP. Data are shown as mean ± SEM. *P <0.05; **P <0.005 compared to unstimulated PBMC.

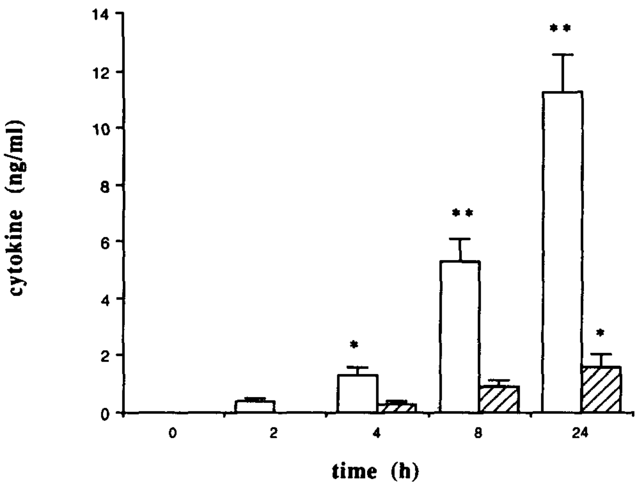

Figure 2. Time course of IL-1Ra (*open bars*) and IL-1β (*hatched bars*) production by PBMC stimulated with 300 μg/ml CRP. Data are derived from the cells of three donors and are shown as mean ± SEM. *$P<0.05$; **$P<0.005$ from $t = 0$.

bodies completely suppressed IL-2–induced IL-1Ra and IL-1β production but did not influence CRP-induced IL-1Ra and IL-1β synthesis (Table 1).

Induction of IL-1Ra and IL-1β in PBMC by α_1-AT and FVYLI. Both α_1-AT and FVYLI induced concentration-dependent IL-1Ra and IL-1β synthesis (Fig. 3). α_1-AT at a concentration of 10^{-7} M induced significant amounts of IL-1Ra (1.9 ± 0.2 ng/ml), whereas IL-1β production required a higher concentration (10^{-6} M) of α_1-AT (Fig. 3 *A*). At α_1-AT concentrations of 10^{-6} and 10^{-5} M, the induced IL-1Ra concentrations were approximately eightfold those of IL-1β. The effects of α_1-AT on IL-1Ra and IL-1β production were almost completely blocked by a specific anti–α_1-AT antibody that had no effect on LPS-induced cytokine synthesis (Table 2). Despite the fact that α_1-AT is known to bind to the serpin–enzyme complex (SEC) receptor on human monocytes as a complex with elastase (21), the addition of leukocyte elastase did not enhance the inductive effects of α_1-AT. In fact, incubation of PBMC with equimolar concentrations of elastase and α_1-AT induced IL-1Ra and IL-1β levels identical to those obtained with α_1-AT alone (data not shown).

The synthetic pentapeptide FVYLI, the minimal binding sequence for the SEC receptor (22), showed a pattern of cytokine induction similar to that of α_1-AT. At a concentration of 10^{-6} M, significant amounts of IL-1Ra (1.6 ± 0.3 ng/ml) were induced, whereas significant IL-1β production was observed only at 10^{-4} M (Fig. 3 *B*). 10^{-4} M of FVYLI induced as much IL-1Ra and IL-β as 10^{-6} M α_1-AT. The ratio of IL-1Ra to IL-1β was consistently in excess of 5 with each concentration FVYLI tested over 10^{-6} M. The control peptide FVYL showed no significant induction of both IL-

Table 1. *Neutralization of CRP-induced Cytokine Synthesis with Specific Antibodies*

Stimulus	Inhibitor	IL-1Ra	IL-1β
		ng/ml	
CRP (100 μg/ml)	–	7.7 ± 1.1	0.9 ± 0.1
	Control IgG	7.4 ± 1.2	0.8 ± 0.2
	anti–CRP	0.5 ± 0.1*	0.1 ± 0.05*
LPS (100 ng/ml)	–	8.5 ± 1.1	7.4 ± 1.2
	Control IgG	8.0 ± 0.9	6.9 ± 1.2
	anti-CRP	8.3 ± 1.0	7.2 ± 1.1
LPS (100 ng/ml)	–	8.5 ± 1.1	7.4 ± 1.2
	PMB	0.3 ± 0.1*	0.2 ± 0.1*
CRP (100 μg/ml)	–	8.1 ± 1.4	1.0 ± 0.1
	PMB	7.9 ± 1.3	0.9 ± 0.2
IL-2 (1,000 U/ml)	–	7.3 ± 1.4	5.5 ± 1.2
	anti–p75	0.5 ± 0.1*	0.3 ± 0.1*
	anti–IL-2	0.4 ± 0.1*	0.2 ± 0.1*
CRP (100 μg/ml)	–	8.2 ± 1.4	0.9 ± 0.2
	anti–p75	8.1 ± 1.3	1.0 ± 0.2
	anti–IL-2	7.9 ± 1.2	1.1 ± 0.2

PBMC were incubated for 24 h. Data represent mean ± SEM from three experiments. Polymyxin B was used at a concentration of 5 μg/ml. The goat anti–CRP antibody and a nonimmune goat IgG were both used at a concentration of 100 μg/ml. The anti–IL-2 antiserum and anti-p75 IL-2 receptor mAb were used at concentrations of 1,000 U/ml and 100 μg/ml, respectively.
* $P<0.005$ from CRP, IL-2, and LPS alone.

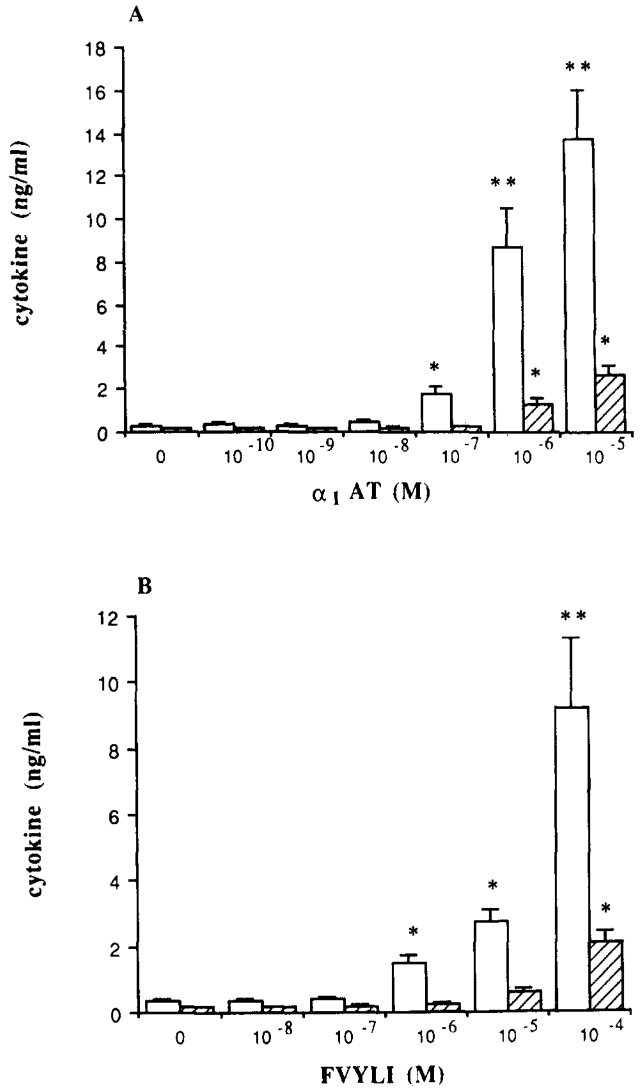

Figure 3. (*A*) Induction of IL-1Ra (*open bars*) and IL-1β (*hatched bars*) by human PBMC incubated with α_1-AT (mean ± SEM; n = 6). $^*P$ <0.05; $^{**}P$ <0.005 compared to unstimulated PBMC. (*B*) Induction of IL-1Ra (*open bars*) and IL-1β (*hatched bars*) by the pentapeptide FVYLI in human PBMC (same donors as *A*) (mean ± SEM; n = 6). $^*P$ <0.05; $^{**}P$ <0.005 compared to unstimulated PBMC.

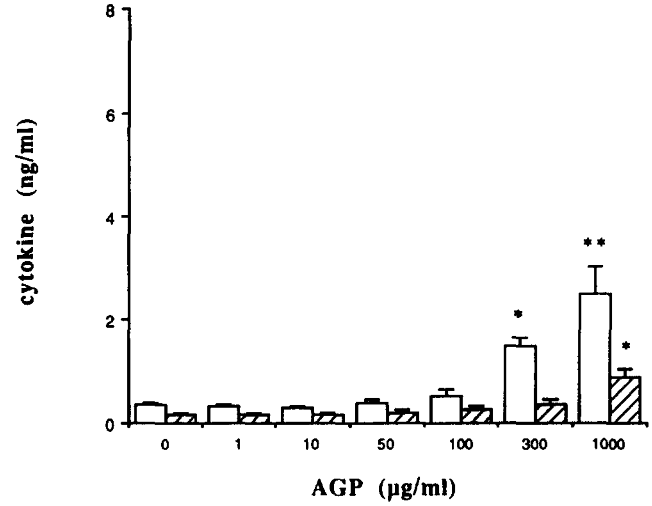

Figure 4. Induction of IL-1Ra (*open bars*) and IL-1β (*hatched bars*) by PBMC incubated with AGP (mean ± SEM; n = 4). $^*P$ <0.05; $^{**}P$ <0.005 compared to unstimulated PBMC.

1Ra and IL-1β; likewise, DMSO at the concentrations used for dissolving the short peptides did not induce cytokine production (data not shown).

Induction of IL-1Ra and IL-1β by AGP. We also tested another APP, AGP, for its potential to induce IL-1Ra and IL-1β. AGP induced significantly less IL-1Ra than CRP or α_1-AT (Fig. 4). In addition, the ratio of IL-1Ra to IL-1β was only 2.4:1. AGP-induced cytokine production was abrogated with a specific antibody, whereas a control antibody showed no effect (Table 2). The anti-AGP IgG had no effect on LPS-induced IL-1Ra or IL-1β synthesis.

Synergistic Effects of CRP and α_1-AT on the Synthesis of IL-1Ra by PBMC. PBMC from three donors were incubated with increasing concentrations of CRP and α_1-AT for 24 h, and the IL-1Ra produced was measured by RIA. Low concentrations of CRP and α_1-AT, which individually induced only modest amounts of IL-1Ra, were highly stimulatory when present simultaneously (Table 3). This synergy was especially evident with 10^{-7} M α_1-AT, which induced only 0.93 ± 0.03 ng/ml IL-1Ra by itself but 3.27 ± 0.35 ng/ml IL-1Ra (P <0.02) in the presence of trivial (10 µg/ml) concentrations of CRP.

Synergistic Effects of CRP, α_1-AT, FVYLI, and AGP with LPS on IL-1Ra and IL-1β Synthesis by PBMC. PBMC were incubated with increasing concentrations of LPS and either 50 µg/ml CRP, 10^{-7} M α_1-AT, 10^{-6} M FVYLI, or 100 µg/ml AGP. LPS induced comparable amounts of IL-1Ra and IL-1β (Figs. 5 and 6). Each APP tested as well as the peptide FVYLI were synergistic with low concentrations (10 pg/ml) of LPS in the induction of IL-1Ra (Fig. 5) and IL-1β (Fig. 6). PBMC incubated with LPS (10 pg/ml) plus APP synthesized significantly more IL-1Ra and IL-1β than with LPS alone (P <0.001 for each APP tested). DMSO at concentrations used to dissolve FVYLI had no effect on LPS-induced IL-1Ra and IL-1β synthesis (data not shown).

Discussion

Several hepatic APP have been shown to either induce or augment the synthesis of IL-1, TNF, and IL-6 in vitro (23–25), suggesting that APP contribute to the development of an inflammatory response. Despite these in vitro data, several animal models exist in which the prior initiation of an acute phase response or the administration of a specific APP have been shown to limit the severity of inflammation or to protect against the lethal effects of LPS, TNF, or IL-1 (2–9). The mechanism underlying these antiinflammatory effects is unclear.

Table 2. *Effect of Specific Antibodies on α_1-AT- and AGP-induced IL-1Ra and IL-1β Synthesis*

Stimulus	Antibody	IL-1β	IL-1Ra
		ng/ml	
α_1-AT (10^{-6} M)	–	8.7 ± 1.4	1.4 ± 0.4
	Control IgG	8.3 ± 1.2	1.3 ± 0.3
	α_1-AT	1.9 ± 0.2*	0.3 ± 0.1*
LPS (100 ng/ml)	–	8.5 ± 1.1	7.4 ± 1.2
	Control IgG	8.6 ± 1.4	7.0 ± 0.8
	α_1-AT	7.9 ± 1.0	7.3 ± 0.9
AGP (300 μg/ml)	-	1.8 ± 0.4	0.4 ± 0.2
	Control IgG	1.9 ± 0.3	0.5 ± 0.2
	AGP	0.3 ± 0.1*	0.2 ± 0.1
LPS (100 ng/ml)	-	8.5 ± 1.1	7.4 ± 1.2
	Control IgG	8.7 ± 1.0	8.1 ± 0.9
	AGP	9.0 ± 0.9	8.3 ± 1.2

PBMC were incubated for 24 h. Data represent mean ± SEM from three experiments. Rabbit anti–α_1-AT and AGP antibodies as well as nonimmune IgG were used diluted 1/100.
* P <0.005 from α_1-AT and AGP alone.

CRP has been shown to induce the synthesis of IL-1α, IL-1β, TNFα, and IL-6 in human PBMC and alveolar macrophages (23, 24), suggesting that one of its primary functions is the amplification of inflammatory responses. However, our studies demonstrate that CRP is, in fact, a more potent inducer of the antagonist IL-1Ra. In this respect, the synthetic response to CRP more closely resembles the response to immune complexes or aggregated IgG than the response to LPS or IL-2, both of which induce approximately equal amounts of IL-1Ra and IL-1β (Table 1). The conten-

Table 3. *Synergistic Effects of CRP and α_1-AT on the Synthesis of IL-1Ra by PBMC*

		α_1-AT				
		0	10^{-9}	10^{-8}	10^{-7}	10^{-6}
	CRP	IL-Ra				
	µg/ml	*ng/ml*				
Exp. 1	0	0.21	0.24	0.32	0.88	4.7
	1	0.22	0.38	0.32	1.2*	3.5
	10	0.49	0.3	0.41	2.7*	5.7*
	100	4.4	4.8	5.9*	9.2*	8.7
Exp. 2	0	0.38	0.37	0.52	0.99	5.2
	1	0.42	0.26	0.45	1.3	4.6
	10	0.51	0.63	1.6*	3.2*	7.8*
	100	3.6	3.2	4.8*	8.9*	7.9
Exp. 3	0	0.27	0.21	0.26	0.93	4.4
	1	0.33	0.27	0.32	1.6*	4.5
	10	0.48	0.59	0.69	3.9*	8.2*
	100	3.8	3.6	6.1*	9.7*	8.9*

* IL-1Ra values greater than the sum of those achieved with CRP and α_1-AT individually.

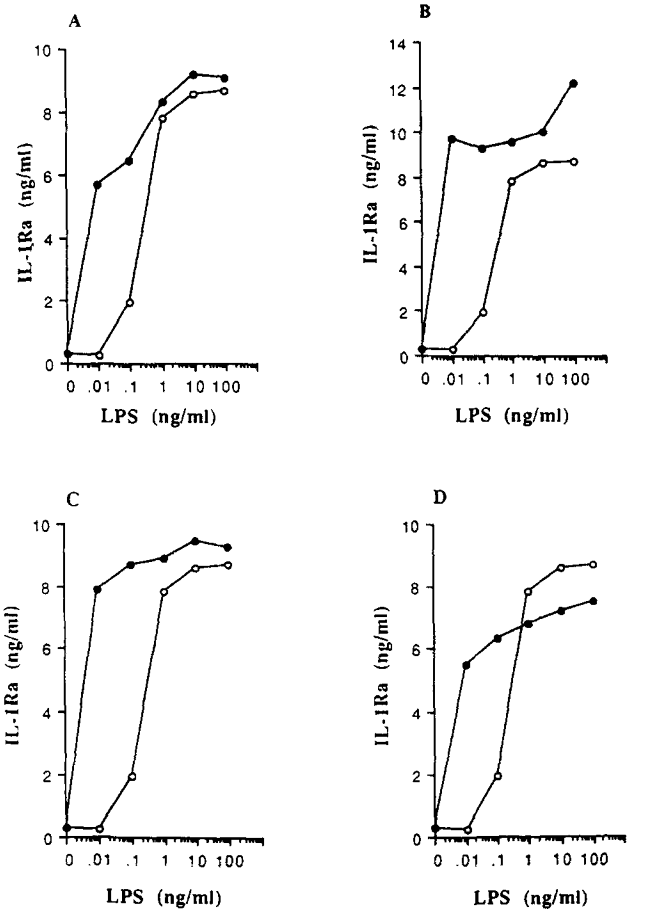

Figure 5. Effects of (*A*) CRP (50 μg/ml), (*B*) α_1-AT (10^{-7} M), (*C*) FVYLI (10^{-6} M), and (*D*) AGP (100 μg/ml) on LPS-induced synthesis of IL-1Ra by human PBMC (O, LPS alone; ●, LPS + APP). One representative experiment from three performed is shown.

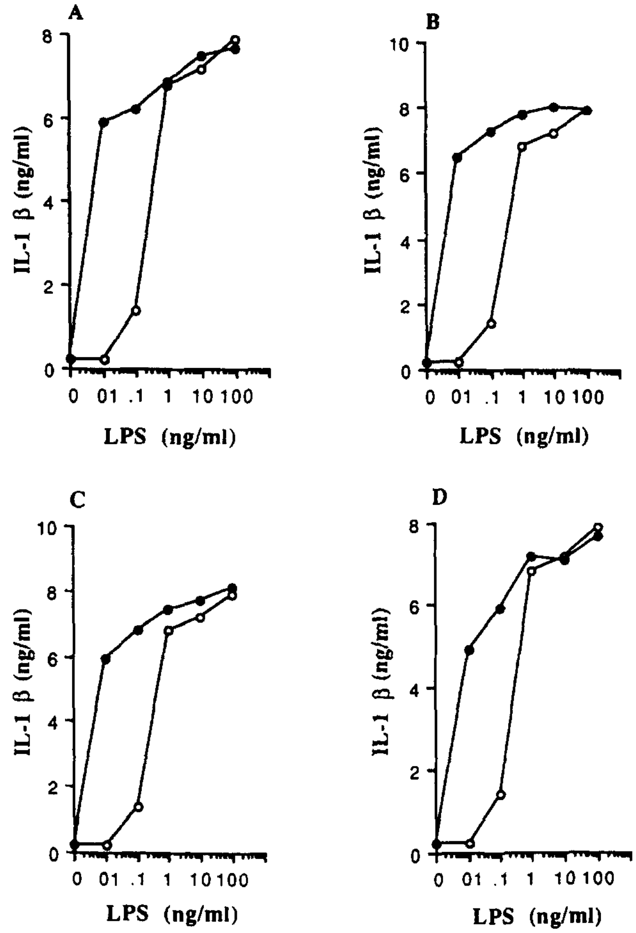

Figure 6. Effects of (*A*) CRP (50 μg/ml), (*B*) α_1-AT (10^{-7} M), (*C*) FVYLI (10^{-6} M), and (*D*) AGP (100 μg/ml) on LPS-induced synthesis of IL-1β by human PBMC (same donors as in Fig. 5) (O, LPS alone; ●, LPS + APP). One representative experiment from three is shown.

tion that CRP is primarily an antiinflammatory mediator is supported by data from animal studies in which high serum levels of CRP resulting either from prior turpentine treatment or as a result of the expression of a transgene protect mice from lethal doses of LPS (2, 3). The morbidity associated with sepsis is thought to be due to endogenous platelet-activating factor, a phosphorylcholine-containing phospholipid (26). As suggested by Xia et al. (3, 27), the binding of platelet-activating factor through its phosphorylcholine moiety may indeed be an important mechanism underlying the protective effect of CRP. However, several studies have shown that IL-1Ra exerts a similar protective effect in LPS-treated animals and it is therefore equally plausible that the induction of IL-1Ra is the primary mechanism by which CRP mediates its protective effects (12, 13, 28).

The hepatic APP α_1-AT is a member of the serine protease inhibitor (serpin) family. α_1-AT is, in fact, the major circulating inhibitor of neutrophil elastase and a deficiency of this inhibitor is associated with chronic inflammation in the lung and liver with premature emphysema and cirrhosis (29). α_1-AT–elastase complexes are known to bind to SEC receptors present on hepatocytes, the result of which is the up-regulation of α_1-AT synthesis in the liver (21). A similar receptor has been described on neutrophils and its engagement results in chemotaxis (30). We have shown that stimulation of PBMC with prepared α_1-AT–elastase complexes, α_1-AT alone, or the pentapeptide FVYLI induces the preferential synthesis of IL-1Ra, presumably a result of signaling through the SEC receptor or a related structure. The activity of α_1-AT in the absence of exogenous elastase is most likely due to the formation of a complex with endogenous elastase (31).

SEC receptors are involved in the clearance of several distinct SECs including thrombin–antithrombin III, thrombin–heparin cofactor II, as well as α_1-AT-elastase (32). Our results suggest that SEC receptors not only remove endogenous proteases such as elastase from the circulation but may trigger the generation of an important IL-1 antagonist. The development of pulmonary fibrosis in response to the chemotherapeutic agent bleomycin is largely due to endogenous IL-1 and can be prevented by the administration of IL-1Ra or α_1-AT (8, 33). The role of IL-1 in tissue fibrosis and the ability of SECs to stimulate IL-1Ra synthesis suggest that the cirrhosis associated with α_1-AT deficiency may not be entirely due to inadequate clearance of elastase but also to reduced IL-1Ra synthesis.

AGP is another hepatic APP implicated in the regulation of inflammation. AGP undergoes extensive posttranslational modification, including the acquisition of sialyl-Lewis-X containing glycans during an acute phase response (34). The expression of the sialyl-Lewis-X epitope may allow AGP to bind to selectins present on leukocytes and endothelial cells. Such an interaction might interfere with leukocyte emigration and thereby suppress inflammation (34). Although AGP is known to potentiate LPS-induced secretion of proinflammatory cytokines by human monocytes (25), it also induces the production of an IL-1 inhibitor by murine macrophages (35). The induction of this inhibitor appears to depend on the extent of glycosylation (35). Our studies strongly suggest that this IL-1 inhibitor is IL-1Ra. The AGP preparation used in our investigation was not as potent an inducer of IL-1Ra as CRP or α_1-AT. However, we have not surveyed a wide range of AGP preparations, in particular material isolated from sera of patients with inflammatory diseases. It is conceivable that the weak response to our AGP preparation could be due to inadequate glycosylation.

We have shown that three distinct, structurally unrelated APP are potent inducers of the antiinflammatory cytokine IL-1Ra and have suggested that these inductive effects may account for some of their antiinflammatory properties. These same agents, however, are highly synergistic with low concentrations of LPS in inducing the synthesis of both IL-1β and IL-1Ra. In fact, the relative amounts of IL-1Ra and IL-1β generated in response to the APP/LPS combination are similar to those induced by high concentrations of LPS alone. These findings indicate that APP may function in a dual role, amplifying inflammatory responses when the inciting pathogen is present within the host and down-modulating the response when the pathogen has been eradicated. Our results suggest that modulation of the profile of cytokines generated under different circumstances may be the means by which such a dual function is achieved.

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Address correspondence to James W. Mier, M.D., Division of Hematology-Oncology, Department of Medicine, New England Medical Center, 750 Washington Street, Box 245, Boston, MA 02111.

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